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BURNS, R EXAMINER

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892. 1 page
2. ☒ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☒ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-14 are pending in the application
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-14 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Applicant is encouraged to file an information disclosure statement including (1) a form PTO-1449, "Information Disclosure Citation" listing patents, publications and other information material to the instant application; (2) a concise explanation of the relevance of each listed item; (3) a copy of each listed item; and (4) a disclosure of related co-pending applications. See 37 C.F.R. §§ 1.97-1.98.

Claims 11 and 13-14 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 11 is vague and indefinite in the recitation "(ATCC Deposit _____)" since it is entirely unclear to what the deposit refers. Amendment of claim 11 to recite the specific A.T.C.C. Accession No. of the deposit would obviate this rejection. Claim 13 is vague and indefinite in the recitation "and lymphoid on monocyte lineage cell lines" since it is not clear what cell lines are described. It is believed that this is a typographical error and should recite "or" rather than "on" as claimed. If so, amendment of claim 13 to change the "on" to "or" would obviate this rejection.

35 U.S.C. § 101 reads as follows:

> **Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.**

Claims 1-10 and 12-14 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1-10 and 12-14, as written, do not sufficiently

distinguish over anti-TNF as it exists naturally because claims 1-10 and 12-14 do not particularly point out any non-naturally occurring differences between the claimed antibody compositions and the structure of naturally occurring anti-TNF antibodies. The claims, as written read on, for example, a human being, since a human being is a composition comprising human antibodies.

In the absence of the hand of man, the naturally occurring antibodies are considered non-statutory subject matter (Diamond v. Chakrabarty, 206 U.S.P.Q. 193 (1980)). It should be noted that the mere purity of a naturally occurring product does not necessarily impart patentability (Ex parte Siddiqui, 156 U.S.P.Q. 426 (1966)). However, when purification results in a new utility, patentability is considered (Merck Co. v. Chase Chemical Co., 273 F.Supp 68 (1967), 155 USPQ 139, (District Court, New Jersey, 1967)). Amendment of the claims to recite "a composition comprising a human monoclonal antibody that binds to human tumor necrosis factor alpha" would obviate this rejection.

Claims 1-14 are rejected under 35 U.S.C. § 101 because the claimed invention lacks patentable utility. A careful reading of Applicant's specification has not revealed any statements or teachings setting forth the utility of the claimed invention. While Applicant has discussed at some length the characteristics of the claimed B5 antibody, Applicant does not appear to have disclosed an intended utility for the claimed invention. In the absence of any such statement of utility, the claims are rejected.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most**

nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure. As set forth above in the rejection under 35 U.S.C. § 101, the specification lacks sufficient teachings to establish that the claimed invention has a patentable utility. In the absence of such teachings establishing utility, one of ordinary skill in the art would not be able to use the claimed invention without undue experimentation. See In re Fouche, 169 USPQ 429 at 434 (CCPA 1971). "If the application fails as a matter of fact to satisfy 35 U.S.C. § 101, then the application also fails as a matter of law to enable one of ordinary skill in the art to use the invention under 35 U.S.C. § 112." In re Ziegler, 26 USPQ2D 1600 at 1603, (CAFC 1993).

Claims 1-14 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention. The specification contains blank spaces on page 11, lines 11-12 referring to the deposited microorganism. The specification should not contain such blank areas. Amendment of the specification to properly recite the necessary deposit information would obviate this objection.

Claims 1-14 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure without complete evidence either that the claimed biological materials are known and readily available to the public or complete evidence of the deposit of the biological material.

The specification lacks complete deposit information for the deposits of the hybridoma cell line designated B5 producing the B5 human monoclonal antibody. Because it is not clear that antibodies possessing the properties of the B5 human monoclonal antibody, particularly the fact that it is a human autoantibody to human TNF which can also bind mouse TNF as well as cell surface TNF, are known and publicly available or can be reproducibly isolated from nature without undue experimentation and because the best mode disclosed by the specification requires the use of the B5 antibody, a suitable deposit for patent purposes is required. Accordingly, filing of evidence of the reproducible production of the cell lines and antibodies claimed, or filing of evidence of deposits commensurate in scope with the claims is required. Without a publicly available deposit of the cell line, one skilled in the art could not be assured of the ability to practice the invention claimed. Note that the best mode is not satisfied by a written disclosure unless the exact embodiment is reasonably reproducible from that disclosure. If reproducibility of the cell line is not established, failure to deposit the cell line would result in concealment of the best mode contemplated by applicant for carrying out the invention. In re Sherwood, 615F.2d 809, 204 U.S.P.Q. 537 (CCPA 1980).

Applicant's referral to the deposits of the B5 hybridoma, listed on page 11, lines 10-12, is an insufficient assurance that all required deposits have been made and all conditions properly met.

If the deposits were made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicants, assignees, or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number is required. The affidavit, declaration or attorney's statement should specifically state that:

1) the deposits have been accepted by an International Depository Authority under the provisions of the Budapest Treaty;

2) that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application; and

3) that the deposit will be replaced if viable samples cannot be dispensed by the depository.

This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is also required.

If the deposits have not been made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 C.F.R. §§ 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees, or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number specifically stating that:

(1). during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request;

(2). all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application;

(3). the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(4). the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is also required.

If the deposit was made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the hybridoma described in the specification as filed is the same as that deposited in the depository. Corroboration may take the form of a showing of a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

Applicant's attention is directed to 37 C.F.R. § 1.801-1.809 and In re Lundak, 773 F.2d. 1216, 227 U.S.P.Q. 90 (CAFC 1985) for further information concerning the Rules and Regulations for Deposit of Biological Materials for Patent Purposes.

Claims 1-14 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure. Applicant has only taught the production and characterization of the B5 human monoclonal antibody to tumor necrosis factor α. Applicant has not provided evidence of other human antibodies to TNF or, more particularly, of other human monoclonal antibodies having the properties of B5 such as binding to cell surface TNF and down-regulating TNF secretion. It is well known in the art that the production of monoclonal antibodies is unpredictable and that there is a low probability of obtaining the same or similar monoclonal antibodies to a particular antigen. This low probability, together with the characteristics of the B5 human monoclonal antibody discussed above, would not allow one skilled in the art to produce the monoclonal antibodies of the claimed invention or similar antibodies without undue experimentation. This lack of enablement is compounded by the fact that Applicant required a CMV positive donor (see page 11, lines 4-14) and that "it is unclear whether or not the CMV seropositive donor origin of B5 mAb is significant" (see page 37, lines 6-7). Thus, it is not clear from the teachings of the specification that one of ordinary skill in the art could obtain additional peripheral blood lymphocytes necessary for human hybridoma production, or even what criteria would be significant for identifying potential lymphocyte donors having anti-TNF human antibodies. As the claims must be commensurate in scope with the enablement provided by the specification, the claims should be limited to the B5 hybridoma producing the B5 human monoclonal antibody to TNFα.

Claims 1-10 and 12 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

The following is a quotation of the appropriate paragraphs of

35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office Action:

> **A person shall be entitled to a patent unless--**
>
> **(b) the invention was patented or described in a printed publication in this country or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.**

Claim 12 is rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Bringman et al. (R). Bringman et al. teaches high affinity monoclonal antibodies which recognize and neutralize TNF (see page 495, Table 1, first five clones). Each of these murine monoclonal antibodies has a titer which favorably compares with the other monoclonal antibodies and thus meets the limitations of the claims. Thus, the reference fully discloses to the public that which is claimed in this application and, inasmuch as this disclosure was made more than one year prior to the filing of this patent application, the issuance of a patent is barred.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> **A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.**
>
> **Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter**

and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligations under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claim 12 is rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over either Socher et al. (S). Socher et al. teaches the production of rabbit antisera which specifically recognizes and neutralizes human TNF. Socher et al. is silent with respect to the titer of the antisera compared to three mouse antibodies as recited in the claim. However, as shown on page 8831, Table 1, the antisera of Socher et al. exhibited very high titers by ELISA and one of ordinary skill in the art would reasonably conclude that these very high titers would be comparably to a panel of three mouse anti-TNF antibodies, particularly as the claim does not specify which mouse antibodies are used and therefore allows a broad range of activity. Since the Patent Office does not have the facilities for examining and comparing applicants' antibody preparation with the antibodies of the prior art reference, the burden is upon applicants to show an unobvious distinction between the material, structural and functional characteristics of the claimed antibodies and the antibodies of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 1977).

Claims 1-11 and 13-14 appear free of the art. Claims 1-11 and 13-14 are all directed to human antibodies to human TNF. The prior art does not appear to recognize the existence of human

autoantibodies to human TNF. In the absence of evidence establishing the existence of human antibodies to TNF, one of ordinary skill in the art would not have a reasonable expectation of success in producing human monoclonal antibodies specific for TNF. Thus the prior art does not appear to either anticipate or fairly suggest the claimed invention. Should Applicant be aware of prior art teachings establishing the existence of human autoantibodies to TNF, Applicant is requested to submit such references for the Examiner's consideration.

No claim is allowed.

Papers relating to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center number is (703) 308-4227. Papers may be submitted Monday-Friday between 8:00 am and 4:45 pm (EST). Please note that the faxing of such papers must conform with the Notice published in the Official Gazette, 1096 OG 30, (November 15, 1989).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert D. Budens whose telephone number is (703) 308-2960.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert D. Budens
Patent Examiner
Art Unit 1806

rdb
September 23, 1993